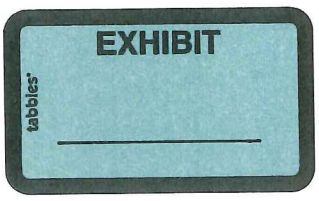
EXHIBIT 621

My name is Dr. Reynolds Delgado, I do hereby state by and through this declaration to the following facts and opinions. This declaration correctly and truthfully states the facts and opinions that I hold regarding the above referenced case and I do hereby swear under oath to the following:

I have read the Memorandum In Support of Defendants' Motion for Summary Judgment. I respond to the following criticisms made by counsel for the Defendants in the above referenced case as follows:

First, the Defendants claim that I used two different methodologies, one while I was treating Ms. Vega and another after her death. This is incorrect. I used the same methodology to arrive at my opinions regarding this case as I used in caring for and treating Ms. Vega. This is the methodology I have used every day in my clinical practice in the field of cardiology. What changed between the time I treated Ms. Vega and my final conclusion regarding the cause of Ms. Vega's death is the data. That new data allowed me to come to a conclusion about why Ms. Vega had such a dramatic unexpected decline in her condition that resulted in her death. I had been treating Ms. Vega for many years. It is true that Ms. Vega had serious heart failure problems but we had successfully managed her care in anticipation of her heart transplant. Suddenly, all the treatment strategies that had worked before, stopped working. While treating her, this was a mystery to the entire treatment team. No one on the team suspected that out of specification Digitek tablets were making the difference and causing her to be unresponsive to proven methods of medical management. It was only after she passed and I was asked to review her case, taking into consideration the possibility that out of specification Digitek had caused the dramatic acceleration of her heart failure. It was then that I discovered that in all probability, out of specification Digitek was the variable that explained what had been unexplainable at the time I was treating her. I used the same diagnostic, clinical, medical and scientific methodologies I use every day as a treating physician specializing in treating patients with advanced heart failure in reaching the conclusion that Digitek was a cause of Ms. Vega's death.

When I reviewed Ms. Vega's course after her death, I also discovered that Dr. Kirkwood Adams had published an article that documented increased mortality in women who took digoxin. Dr. Adams' work demonstrated that digoxin levels, especially in women, well below what physicians have historically thought to be toxic levels, had adverse effects. This leads me to the Defendants second misconception about the dangers of digoxin and my opinion in this case. Historically, physicians have thought of digoxin toxicity as being the only adverse event caused by overdoses of digoxin. What the Adams work taught us was that digoxin, especially in women, at levels found in Ms. Vega, can have an adverse effect on patients in a way that is different than digoxin toxicity. Adams work demonstrated that there is another effect of digoxin, at pre-toxic levels, that worsens heart failure. In a patient such as Ms. Vega, the balance between stability and the tipping point of a crash is narrow. For years we had successfully managed Ms. Vega using digoxin along with other successful methods of medical management. She was on the heart transplant list. She would not have qualified for a heart transplant in our institution if we had not had her condition under control and stable. Something changed. Dr. Adam's paper explains this change. At digoxin levels as low as 1.2 ng/ml, Dr. Adams demonstrated a significant increase in



mortality due to increased heart failure. Prior to Dr. Adam's work, digoxin toxicity, which is different than increased heart failure, was thought to be the only adverse effect of overdoses of digoxin. Dr. Adams demonstrated that not only can a patient suffer from digoxin toxicity but that increased levels of digoxin can actually worsen and accelerate heart failure. Dr. Adam's work was so powerful that it led to a change in the clinical guidelines followed by cardiologists and clinicians in this country. The Heart Failure Society of America adopted new guidelines for digoxin levels, citing Dr. Adam's work, setting the limit of safe use of digoxin at less than 1.0 ng/ml preferably .7 to .9 ng/ml. **Ex.1** Additionally, American College of Cardiology/ American Heart Association (ACC/AHA) Practice Guidelines were amended in 2009 regarding the risks of digoxin. **Ex.2** The ACC/AHA noted in these amended guidelines that "there is a concern that levels of digoxin that previously had been considered to be in the therapeutic range, (up to 2 ng/mL) may exert deleterious cardiovascular effects in the long term, even though such levels appear to be well tolerated in the short term." Citing the work of Dr. Adams, the ACC/AHA went on to note, "These observations have raised the possibility that digoxin doses and serum digoxin concentrations that are generally considered by physicians to be safe may adversely affect the heart". Further, the ACC/AHA downgraded the recommendation for use of digoxin from a Class I to Class IIa noting that, "If digitalis were a new drug with clinical trials showing a very narrow risk/benefit ratio (especially for potential use in the aging population) and no mortality benefit, it would clearly not be considered for Class I recommendation." This means that the accepted medical practice that has developed based on the foundation of Dr. Adams' work, after full review by the ACC/AHA, led to the downgrading of the advisability of the use of digoxin in patients similar to Mimi Vega. Mimi Vega's digoxin levels were measured at 1.2 ng/ml. Dr. Adam's work, based on a retrospective look at the data collected in largest prospective clinical trial on digoxin ever conducted, shined a new light on the cause of Mimi Vega's sudden and unexpected dramatic decline and accelerated heart failure. Mimi Vega had been managed successfully with digoxin for many years. Historically, her digoxin levels had been measured lower than 1.2 ng/ml. When her levels rose to 1.2 ng/ml, since this was still in the normal range, there was no reason to suspect that she was declining because of digoxin toxicity. Nor was it known to me, prior to review of Dr. Adams' work, that digoxin levels as low as 1.2 ng/ml could cause increased heart failure. In fact, the Defendants are right, she was not toxic as a result of the increased digoxin levels, but as Dr. Adams demonstrated, the increased levels of digoxin caused her heart failure to dramatically worsen. This is what we see in the new abnormalities of her EKG results. The question was, why did she suddenly go from stable to steep decline? Nothing else changed. The Adam's paper answers this question. The increased digoxin levels of 1.2 ng/ml caused her heart failure to dramatically worsen. Ms. Vega's prescribed dose of digoxin did not change. Her digoxin levels had not been historically variable. The only explanation for the 1.2 ng/ml digoxin level was that we thought she was getting the correct dose when in reality she was getting an overdose. The realization that digoxin levels of 1.2ng/ml could cause worsening heart failure and eventual death, as demonstrated by Dr. Adam's work, led to the inescapable conclusion that the variable that I had not considered during her treatment was an overdose of digoxin caused by out of specification Digitek tablets.

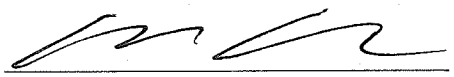
The Defendants focus on the "confidence level" chart found in Dr. Adams' work and compare it to "relative risk", a term of art that is used in epidemiological studies. They further mischaracterize Dr. Adams' paper as a retrospective study. Dr. Adams' work is neither an epidemiological study nor a restrospective study. Dr. Adams' work is a retrospective look at a prospective clinical trial, commonly known as the "dig trial". The data base used by Dr. Adams

is the most extensive data base ever collected concerning the effects to digoxin. The digoxin clinical trial, upon which Dr. Adams drew his data, was a double blind clinical trial prospectively investigating the effects of digoxin therapy, both adverse and therapeutic. As I mentioned above, Dr. Adams' work was so persuasive that the Heart Failure Society of America (HFSA) adopted new guidelines lowering the recommended safe digoxin level to below 1.0 ng/ml preferably .7 to .9 ng/ml. The HFSA evaluated the strength of Dr. Adam's findings in terms of probability using a scale A-C. The HFSA guideline process uses a hierarchy assigning "Relative Weight" to types of evidence it relies upon in deciding to change the guidelines. The strongest type of evidence in this hierarchy, level A, is randomized, controlled clinical trials. The data base relied upon by Dr. Adams was such a clinical trial. The second strength of evidence in the HFSA hierarchy that is relied upon by the HFSA in considering a change in the guidelines, level B, is cohort and case controlled studies. The last on the hierarchy of types of evidence that are considered by the HFSA, level C, are expert opinions, observational studies-epidemiologic findings and safety reporting from large scale use. The HFSA ranked Dr. Adams' paper as level B evidence that digoxin levels in excess of 1 ng/ml are not recommended. The HFSA rated the strength of Dr. Adams' work as greater than epidemiological findings. Finally, in an email to one of the Defendants' experts, Dr. Adams clearly stated the import of his findings when he said, "It is clear that conc (concentration) at higher end in traditional therapeutic range are ***very likely*** **unsafe."Ex.3** Dr. Adams is an experienced investigator. He knows the difference between "relative risk" in the epidemiological setting and a confidence level used in the context of his paper. I also know the difference. Further, Dr. Adams' work was published in a Tier I, peer reviewed medical journal, The Journal of American College of Cardiology. I am familiar with this publication. This publication does not print purely retrospective studies. The peer review for this publication is rigorous. The reliability, including the confidence level of the results, would not have been published if Dr. Adams had not established the probability of his findings. I know that this journal independently verifies the statistical analysis and basis for all printed findings. I agree with Dr. Adams, what we have long thought to be safe levels of digoxin are "very likely unsafe". These high end levels, previously thought to be within therapeutic range, are unsafe because they cause sudden death and accelerated heart failure, not because they cause digoxin toxicity. This is what I believe happened to Ms. Vega. She took a double thick Digitek tablet, this drove her digoxin level up to 1.2 ng/ml. Especially for Ms. Vega, this was an unsafe level. She did not suffer digoxin toxicity. The digoxin tipped her heart over its capacity to perform and she died. A double thick tablet of digoxin is the only explanation that is reasonably probable in this case.

The Adams work revealed a new danger associated with the narrow therapeutic window for digoxin. Put simply, Adams work revealed that once believed safe and therapeutic levels of digoxin aggravate and accelerate heart failure in some patients. This phenomenon has come to be understood, in lay terms, as the "candle that burns twice as bright, burns half as long" effect. Digoxin does not cure heart failure. It lessens the symptoms. It does this by causing the heart to beat stronger and sometimes faster. In an already weakened heart, if you work it too hard suddenly with an unexpected dose of digoxin, the heart failure can get worse instead of better. Another way to understand this phenomenon is to think of the long distance runner who hits the proverbial wall. The body just cannot go any further. Dr. Adams demonstrated that digoxin

levels over 1 ng/ml can cause the heart to pass the point of being able to function properly, ie fail, and that can lead to death, not from digoxin toxicity, but from heart failure. This is what I saw clinically and was evidenced by the sudden changes and new abnormalities on Ms. Vega's EKG. Dr. Adams work was so persuasive that it changed the recommended safe levels for digoxin therapy in the United States and the to some extent the world.

The Defendants' attorneys talk extensively about drug interactions and speculate that other drugs may explain Ms. Vega's dramatic decline and death. They also speculate that other drugs may explain Ms. Vega's elevated digoxin level of 1.2 ng/ml. These arguments are scientifically flawed. While drug interactions may cause a digoxin level to rise as tested in a laboratory, this rise in test results does not make the digoxin act any differently for the patient. For example, the use of some drugs may cause a digoxin serum level that is actually .7 ng/ml test in the lab at 1ng/ml. However, as far as the patient's body is concerned, the amount of digoxin is still the same and the increased test result will not cause the digoxin to act any differently for the patient. The argument that other drugs caused Mimi Vega's digoxin serum level to appear artificially high, does not take into account what actually happened to Mimi Vega. She suffered a dramatic, unexpected acceleration of her heart failure. The sudden change in her condition is best explained, if not only explained, by an increase in the amount of digoxin in her body as a result of an overdose of Digitek. The same can be said for the Defendants' speculation that somehow the use of Milrinone was a cause of Ms. Vega's decline. The dose of Milrinone for Ms. Vega was constant and steadily administered intravenously. There is no evidence that this dose ever lost its efficacy. I have personally maintained patients similar to Ms. Vega on Milrinone for years without the drug losing its efficacy. The Defendants argument that the use of Milrinone contributed to the cause of Ms. Vega's demise is pure speculation and not based on any evidence.



Dr. Reynolds M. Delgado

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Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

St. Paul, Minnesota

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ABSTRACT

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, reduced quality of life, and a complex therapeutic regimen. Knowledge about HF is accumulating so rapidly that individual clinicians may be unable to readily and adequately synthesize new information into effective strategies of care for patients with this syndrome. Trial data, though valuable, often do not give direction for individual patient management. These characteristics make HF an ideal candidate for practice guidelines. The 2010 Heart Failure Society of America comprehensive practice guideline addresses the full range of evaluation, care, and management of patients with HF.

Key Words: Heart failure, practice guidelines.

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The document should be cited as follows: Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WHW, Teerlink JR, Walsh MN. Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16:475–539.

A copy of the HFSA Comprehensive Heart Failure Practice Guideline can be found at www.onlinejcf.com

See page 506 for disclosure information.

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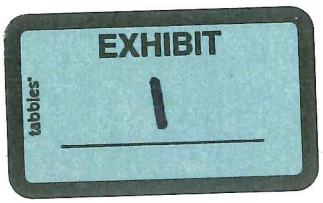

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Section 1: Development and Implementation of a Comprehensive Heart Failure Practice Guideline

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, poor quality of life, multiple comorbidities, and a complex therapeutic regimen. Knowledge about HF is accumulating so rapidly that individual clinicians may be unable to readily and adequately synthesize new information into effective principles of care for patients with this syndrome. Trial data, though valuable, often do not give adequate direction for individual patient management.

Given the complex and changing picture of HF and the accumulation of evidence-based HF therapy, it is not possible for the clinician to rely solely on personal experience and observation to guide therapeutic decisions. The situation is exacerbated because HF is now a chronic condition in most patients, meaning that the outcome of therapeutic decisions might not be apparent for several years. The prognosis of individual patients differs considerably, making it difficult to generalize. Treatments might not dramatically improve symptoms of the disease process, yet might provide important reductions or delays in morbid events and deaths. The assessment of specific therapeutic outcomes is complicated by the potential differential impact of various cotherapies.

The complexity of HF, its high prevalence in society, and the availability of many therapeutic options make it an ideal candidate for practice guidelines. Additional assumptions driving the development of HF guidelines are presented in Table 1.1.

The first HF guideline developed by the Heart Failure Society of America (HFSA) had a narrow scope, concentrating on the pharmacologic treatment of chronic, symptomatic left ventricular dysfunction.[1] It did not consider subsets of the clinical syndrome of HF, such as acute decompensated HF and "diastolic dysfunction," or issues such as prevention. The subsequent comprehensive clinical practice guideline published in 2006 addressed a full range of topics including prevention, evaluation, disease management, and pharmacologic and device therapy for patients with HF.[2] The 2010 guideline updates and expands each of these areas and adds a section on the Genetic Evaluation of Cardiomyopathy published separately in 2009.[3] The discussion of end of life management has also been considerably expanded. Appendix A is a comparison of the 2006

Table 1.1. Assumptions Underlying HFSA Practice Guideline

Clinical decisions must be made.
Correct course of action may not be readily apparent.
Multiple non-pharmacologic, pharmacologic, and device therapies are available.
Reasonably valid methods exist to address knowledge base and evaluate medical evidence.
Data beyond randomized clinical trials exist that enhance medical decision making.
Uncertainties remain concerning approaches to treatment after review of totality of medical evidence.
Expert opinion has a role in management decisions when Strength of Evidence A data are not available to guide management.
A consensus of experts remains the best method of management recommendations when Strength of Evidence A data are not available

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and 2010 guideline, summarizing the modifications, additions, and deletions in the guideline recommendations. Appendix B is a list of acronyms (including clinical trials) used in the 2010 guideline.

HFSA Guideline Approach to Medical Evidence

Two considerations are critical in the development of practice guidelines: assessing strength of evidence and determining strength of recommendation. Strength of evidence is determined both by the type of evidence available and the assessment of validity, applicability, and certainty of a specific type of evidence. Following the lead of previous guidelines, strength of evidence in this guideline is heavily dependent on the source or type of evidence used. The HFSA guideline process has used three grades (A, B, or C) to characterize the type of evidence available to support specific recommendations (Table 1.2).

It must be recognized, however, that the evidence supporting recommendations is based largely on population responses that may not always apply to individuals within the population. Therefore, data may support overall benefit of one treatment over another but cannot exclude that some individuals within the population may respond better to the other treatment. Thus, guidelines can best serve as evidence-based recommendations for management, not as mandates for management in every patient. Furthermore, it must be recognized that trial data on which recommendations are based have often been carried out with background therapy not comparable to therapy in current use. Therefore, physician decisions regarding the management of individual patients may not always precisely match the recommendations. A knowledgeable physician who integrates the guidelines with pharmacologic and physiologic insight and knowledge of the individual being treated should provide the best patient management.

Strength of Evidence A. Randomized controlled clinical trials provide what is considered the most valid form of guideline evidence. Some guidelines require at least 2 positive randomized clinical trials before the evidence for a recommendation can be designated level A. The HFSA guideline committee has occasionally accepted a single randomized, controlled, outcome-based clinical trial as sufficient for level A evidence when the single trial is large with a substantial number of endpoints and has consistent and robust outcomes. However, randomized clinical trial data, whether derived from one or multiple trials, have not been taken simply at face value. They have been evaluated for: (1) endpoints studied, (2) level of significance, (3) reproducibility of findings, (4) generalizability of study results, and (5) sample size and number of events on which outcome results are based.

Table 1.2. Relative Weight of Evidence Used to Develop HFSA Practice Guideline

Hierarchy of Types of Evidence	
Level A	Randomized, Controlled, Clinical Trials May be assigned based on results of a single trial
Level B	Cohort and Case-Control Studies Post hoc, subgroup analysis, and meta-analysis Prospective observational studies or registries
Level C	Expert Opinion Observational studies-epidemiologic findings Safety reporting from large-scale use in practice

Strength of Evidence B. The HFSA guideline process also considers evidence arising from cohort studies or smaller clinical trials with physiologic or surrogate endpoints. This level B evidence is derived from studies that are diverse in design and may be prospective or retrospective in nature. They may involve subgroup analyses of clinical trials or have a case control or propensity design using a matched subset of trial populations. Dose-response studies, when available, may involve all or a portion of the clinical trial population. Evidence generated from these studies has well-recognized, inherent limitations. Nevertheless, their value is enhanced through attention to factors such as pre-specification of hypotheses, biologic rationale, and consistency of findings between studies and across different populations.

Strength of Evidence C. The present HFSA guideline makes extensive use of expert opinion, or C-level evidence. The need to formulate recommendations based on level C evidence is driven primarily by a paucity of scientific evidence in many areas critical to a comprehensive guideline. For example, the diagnostic process and the steps used to evaluate and monitor patients with established HF have not been the subject of clinical studies that formally test the validity of one approach versus another. In areas such as these, recommendations must be based on expert opinion or go unaddressed.

The value of expert opinion as a form of evidence remains disputed. Many contend that expert opinion is a weak form of observational evidence, based on practice experience and subject to biases and limitations. Advocates believe expert opinion represents a complex synthesis of observational insights into disease pathophysiology and the benefits of therapy in broad populations of patients. They stress the value of the interchange of experience and ideas among colleagues, who collectively treat thousands of patients. Through contact with numerous individual health care providers who may discuss patients with them, experts are exposed to rare safety issues and gain insight into the perceptions of practitioners concerning the efficacy of particular treatments across a wide spectrum of HF.

Despite the case that can be made for its value, recommendations based on expert opinion alone have been limited to those circumstances when a definite consensus could be reached across the guideline panel and reviewers.

HFSA Guideline Approach to Strength of Recommendation

Determining Strength. Although level of evidence is important, the strength given to specific recommendations is

including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C)

- Addition of an ARB. (Strength of Evidence = C)
- Addition of an aldosterone antagonist:
  - for severe HF (Strength of Evidence = C)
  - for moderate HF (Strength of Evidence = C)
- Addition of the combination of hydralazine/isosorbide dinitrate:
  - for African Americans (Strength of Evidence = C)
  - for others (Strength of Evidence = C)

Recommendations for Diuretic Therapy

Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for HF when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated "dry" weight goal for the patient. Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function.

7.23 Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). (Strength of Evidence = A) Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF. (Strength of Evidence = B)

7.24 The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B)

Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C)

Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A)

Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.

7.25 Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy. But chronic daily use, especially of metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. (Strength of Evidence = C)

7.26 Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)

7.27 Patients requiring diuretic therapy to treat fluid retention associated with HF generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. (Strength of Evidence = C)

7.28 It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. (Strength of Evidence = C)

Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 2 to 4 lb). (Strength of Evidence = C) (See Section 6 for more information on this topic)

Recommendations for Digoxin

Data from the Digitalis Investigation Group (DIG) trial and the combined databases of several other large trials provide evidence of digoxin's efficacy.[62-68] Digoxin is a drug that is inexpensive and can be given once daily, and it continues to have a therapeutic role in symptomatic patients with HF from reduced LVEF.

7.29 Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:
- NYHA class II-III (Strength of Evidence = B)
- NYHA class IV (Strength of Evidence = C)

7.30 It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)

7.31 Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)

7.32 High doses of digoxin (maintenance dose >0.25 mg daily) for the purpose of rate control are not recommended. (Strength of Evidence = C)

Recommendations for Anticoagulation and Antiplatelet Drugs

Patients with HF are recognized to be at increased risk for arterial or venous thromboembolic events. In addition to atrial fibrillation and poor ventricular function, which promote stasis and increase the risk of thrombus formation, patients with HF have other manifestations of hypercoagulability. Evidence of heightened platelet activation, increased plasma and blood viscosity, and increased plasma levels of fibrinopeptide A, beta—thromboglobulin, D-dimer, and von Willebrand factor have been found in many patients.[69-71] Despite a predisposition, estimates regarding the incidence of thromboemboli in patients with HF vary substantially between 1.4% and 4.2% per 100 patient years.[72-74] Although variability in the reported incidence likely results from differences in the populations studied and the methodology used to identify these events, the consensus is that pulmonary and systemic emboli are not common in HF patients in sinus rhythm. Traditionally, discussion of anticoagulation in patients with HF has centered on warfarin. Antiplatelet agents are often used in patients with HF from ischemic heart disease.

7.33 Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.

7.34 It is recommended that patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus be treated with warfarin (goal INR 2.0-3.0) for the initial 3 months post-MI (Strength of Evidence = B) unless contraindicated.

Other patients with ischemic or nonischemic cardiomyopathy and LV thrombus should be considered for chronic anticoagulation, depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification. (Strength of Evidence = C)

7.35 Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B)

Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)

7.36 Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)

Recommendations for Amiodarone Therapy

Ventricular arrhythmias are common in HF patients, and sudden cardiac death (SCD) continues to account for a significant proportion of the mortality in this syndrome. Many antiarrhythmic drugs have adverse hemodynamic effects sufficient to have negative consequences in patients with HF. Patients with HF are at higher risk for proarrhythmic effects of antiarrhythmic agents. The major role for the use of these agents in HF is to reduce recurrences of symptomatic arrhythmias, usually in patients who have an ICD.[75]

7.37 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A).

7.38 In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)

7.39 It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)

7.40 Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)

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5.6	ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors because of cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	ARBs are recommanded for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	Minor wording modification
5.7	It is recommended that beta blocker therapy be administered to asymptomatic patients with reduced LVEF. (Post MI, Strength of Evidence = B; non–Post MI, Strength of Evidence = C)	Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)	Changed from "is recommended" to "should be considered"
	Section 6: Nonpharmacologic Management and Health Care Maintenance in Patients with Chronic Heart Failure		
6.1	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or obesity should be given specific instructions regarding carbohydrate or caloric constraints. (Strength of Evidence = B)	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or severe obesity should be given specific dietary instructions. (Strength of Evidence = B)	Minor wording modification
6.2	No changes		
6.3	No changes		
6.4	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for such patients. (Strength of Evidence = C)	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for cachexic patients. (Strength of Evidence = C)	Minor wording modification
6.5	No changes		
6.6	Documentation of the type and dose of nutraceutical products used by patients with HF is recommended. (Strength of Evidence = C) Nutraceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increase risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Documentation of the type and dose of naturoceutical products used by patients with HF is recommended. (Strength of Evidence = C) Naturoceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Modification of terminology (nutraceutical to naturoceutical)
6.7	No changes		
6.8	No changes		
6.9	No changes		
6.10	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted after diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted following diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	Minor wording modification

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Appendix A. *(continued)*

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
7.25	No changes		
7.26	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, and renal dysfunction, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Addition of worsening renal function to list of potential side effects
7.27	No changes		
7.28	No changes		
7.29	Digoxin should be considered for patients with LV systolic dysfunction (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: NYHA class II-III (Strength of Evidence = A) NYHA class IV (Strength of Evidence = B)	Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: • NYHA class II-III (Strength of Evidence = B) • NYHA class IV (Strength of Evidence = C)	Modification from "should be considered" to "may be considered", and change in Strength of Evidence
7.30	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL. (Strength of Evidence = C)	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)	Addition of a lower serum concentration range (0.7-0.9 ng/ml), and change in strength of evidence from C to B
7.31	Adequate control of the ventricular response to atrial fibrillation in patients with HF is recommended. (Level of Evidence = B)	Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)	Modification from "is recommended" to "should be considered"
7.32	No changes		
7.33	Treatment with warfarin (goal INR 2.0–3.0) is recommended for all patients with HF and chronic or documented paroxysmal atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack, (Strength of Evidence = C) unless contraindicated.	Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.	Addition of persistent or long-standing atrial fibrillation
7.34	No changes		
Previous 7.35			Deleted from current guideline
7.35 (previous 7.36)	Long-term treatment with an antithrombotic agent is recommended for patients with HF from ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Aspirin is recommended in most patients for whom anticoagulation is not specifically indicated because of its proven efficacy in non-HF patients with ischemic heart disease, its convenience, and lower cost. Lower doses of aspirin (75 or 81 mg) may be preferable because data from 2 trials suggest more frequent worsening of HF at higher doses. (Strength of Evidence = C) Warfarin (goal INR 2.0–3.5) and clopidogrel (75 mg) have also prevented vascular events in post MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Modification of terminology from "antithrombotic" to "antiplatelet"; addition of recommended doses for aspirin. INR range changed to 2.0-3.0

7.36 (previous 7.37)	Routine use of aspirin is not recommended in patients with HF not from ischemic cardiomyopathy and without other evidence of atherosclerotic vascular disease. (Strength of Evidence = C)	Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)	Modification of terminology
Previous 7.38			Deleted from current guideline; addressed in recommendation 7.35
7.37 (previous 7.39)	No changes		
7.38 (previous 7.40)	In patients with HF and an implantable cardioverter defibrillator (ICD), amiodarone may be considered to reduce the frequency of repetitive discharges. (Strength of Evidence = C)	In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)	Modification of wording
7.39 (previous 7.41)	It is recommended that patients taking amiodarone therapy and digoxin or warfarin generally have their maintenance doses of many commonly used agents, such as digoxin, warfarin, and statins, reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	Modification of wording
7.40		Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)	New recommendation
7.41		n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)	New recommendation
	Section 8: Disease Management, Advance Directives, and End-of-Life Care in Heart Failure		
8.1	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. All HF patients benefit from education and counseling, but patients in NYHA functional class III or IV need the most intensive education, whereas patients in NYHA I or II need less intensive education. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. Essential elements of patient education to promote self-care with associated skills are shown in Table 8.1. (Strength of Evidence = B)	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. It is recommended that essential elements of patient education (with associated skills) are utilized to promote self-care as shown in Table 8.1. (Strength of Evidence = B)	Deletion of NYHA specific portion of the recommendation; modification of wording

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ACCF/AHA Practice Guideline: Full Text

2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: *Developed in Collaboration With the International Society for Heart and Lung Transplantation*

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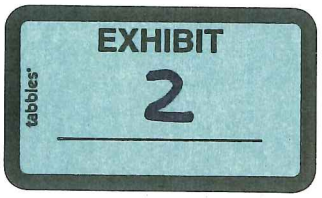

Risks of treatment. When administered with attention to dose and to factors that alter its disposition, digoxin is well tolerated by most patients with HF.[370] The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits.[371–373] The major side effects include cardiac arrhythmias (e.g., ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting), and neurological complaints (e.g., visual disturbances, disorientation, and confusion). Overt digitalis toxicity is commonly associated with serum digoxin levels greater than 2 ng per mL. However, toxicity may occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism coexists.[374,375] The concomitant use of clarithromycin, erythromycin, amiodarone, itraconazole, cyclosporine, verapamil, or quinidine can increase serum digoxin concentrations and may increase the likelihood of digitalis toxicity.[219,376,377] The dose of digoxin should be reduced if treatment with these drugs is initiated. Spironolactone does not inhibit the disposition of digoxin[378]; cross-reactivity of some digoxin antibodies with spironolactone confounded earlier attempts to assess the effect of spironolactone on digoxin clearance. In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digitalis toxicity in elderly patients. Of note, one analysis suggested that women may not benefit from digoxin therapy and may be at increased risk for death with such therapy.[379]

In addition to these established side effects, there is concern that levels of digoxin that previously had been considered to be in the therapeutic range (up to 2 ng per mL) may exert deleterious cardiovascular effects in the long term, even though such levels appear to be well tolerated in the short-term. In one major long-term trial, serum digoxin concentrations in the therapeutic range were associated with an increased frequency of hospitalizations for cardiovascular events other than HF and an increased risk of death due to arrhythmias or MI.[134] These effects neutralized any benefit on survival that might otherwise have been seen as a result of the favorable effect of the drug on HF. These observations have raised the possibility that digoxin doses and serum digoxin concentrations that are generally considered by physicians to be safe may adversely affect the heart.[380] Digoxin should be used with caution or not used at all in post-MI patients, particularly if they have ongoing ischemia.[381]

The writing committee has re-evaluated the evidence pertinent to the value of digitalis therapy in patients with HF. Although no new data or trials using digitalis have emerged since publication of the 2001 guidelines, the writing committee believes that in terms of safety and efficacy, digitalis does not compare favorably with such agents as the aldosterone blockers, to which the writing committee has assigned a Class IIa level of recommendation. If digitalis were a new drug with clinical trials showing a very narrow risk/benefit ratio (especially for potential use in the aging population) and no mortality benefit, it would clearly not be considered for a Class I recommendation. The writing committee, therefore, decided to change the level of recommendation for digitalis glycosides from Class I to Class IIa in the current document.

Mann, Douglas

From: KFA [kfa@med.unc.edu]
Sent: Tuesday, June 22, 2010 9:15 AM
To: Mann, Douglas
Subject: Re:

Doug

I am happy to help if I can. I've not been involved in Digitek cases directly yet so I am not sure how "evidence" is understand in this context.

And we have never published our full analysis of the DIG study - maybe on day.

But we know that CHF Hosp was reduced in original trial w/o consideration of serum concentration.
To me this is against digoxin worsening LV function - which has you know has been a concern about inotropes.

We feel the issue is sudden death not progressive HF at higher concentrations.

This cannot be deduced from our paper alone but is more clear to me if you consider the DIG results on reduction of hospitalization together with our modeling on mortality.

As you note, we use the cut points to give some clinical description to our continuous results. 1.5 is probably more definitive.
It is clear that conc at higher end in traditional therapeutic range are very likely unsafe.

Hope this helps.

Great news on textbook. Sorry for delay on my chapter but I was really happy to have chance to build on original one - best expression concerning guideline methodology and philosophy I've produced yet.

KFA

Mann, Douglas wrote:
>
> Kirkwood
>
> Uncharacteristically I agreed to help with a company with legal case
> while I was still in Houston - it involved Digitek. The plaintiff is
> quoting your article in JACC as the explanation for why the patient
> died (of progressive HF and LVAD complications). It is a bit of a
> stretch.
>
> In reading through your article it seems as though the cut point you
> chose for the lower limits of a dig level that would be harmful was
> 1.2 - this was based on the continuous modeling that you did - but
> appears to have been arbitrary based on your continuous modeling. I
> think you indicate this in the Discussion. I just want to make sure
> that I understand your article correctly, since the plaintiffs
> argument from their expert witness is really focused on the 1.2.
>
> Sorry to pester you on this - just want to make sure that I quote the
> article correctly.